Epigenomics and Maternal Smoking, with Bonnie Joubert and Stephanie London

Ashley Ahearn

Children whose mothers smoked during pregnancy are more likely to have problems like low birth weight, asthma, and possibly obesity, cancer, and high blood pressure. For clues into the mechanism behind these effects, scientists are looking to the epigenome, the personalized set of directions that tells our cells how and when to produce proteins, which is one of the ways gene activity is controlled. In this podcast Stephanie London and Bonnie Joubert discuss the results of their recent study in which they identified a set of genes with methylation changes present at birth in children whose mothers smoked during pregnancy.

AHEARN: It's *The Researcher's Perspective*. I'm Ashley Ahearn.

It's well known that children whose mothers smoked during pregnancy are more likely to have problems like low birth weight, asthma, and maybe obesity, cancer, and high blood pressure. But why? What's the mechanism?

For answers scientists are looking to the epigenome. The epigenome is a personalized set of directions that tells our cells how and when to produce proteins, which is one of the ways gene activity is controlled.

When mothers smoke, how does that affect the way their children's genes function during development—and possibly later on in life? Stephanie London and Bonnie Joubert are uncovering some interesting results.[1]

Stephanie London is the principal investigator for the Genetics, Environment, and Respiratory Disease Group at the National Institute of Environmental Health Sciences.

Bonnie Joubert is a research fellow in the same group.

AHEARN: Thanks for joining me.

LONDON: Thank you.

JOUBERT: Thank you.

AHEARN: Stephanie, tell me a little bit about how you conducted your research. And what did you find?

LONDON: We used a pregnancy cohort called the Norwegian Mother and Child Study, or MoBa[2] for short. And we used cord blood samples from the study. Cord blood is collected at birth from the baby, so it's the baby's DNA. And we looked at whether there

are methylation changes that are related to whether or not the baby's mother smoked. And we were very interested to find, even though we looked in a very hypothesis-free way, that some of the genes that came to the top were ones that we had previously known were very important in the response to compounds that are in tobacco smoke, and in particular, two genes that are in the AhR signaling pathway.

And we found two genes, *AHRR* and *CYP1A1*, that came to the top. And very interestingly, our very top finding in the *AHRR* gene was one that a group very recently (before we published our paper) had looked at adult smokers and nonsmokers,[3] and they found the very same top CpG[4] was differentially methylated in adult smokers compared to adult nonsmokers. And so our finding of differential methylation at the same CpG, in relation to whether your mother smoked, shows that a change that you can find in adult smokers is already present in a baby who is just born because the mother smoked.

AHEARN: Wow.

LONDON: So that was something that was very interesting to us. And then we also identified some novel genes, such as *GFI1*, that had not been previously implicated in the response to compounds in tobacco smoke, but when we look into what's known about *GFI1*, we see that it's involved in many diverse developmental processes, so there's a good reason why it could be related to effects of maternal smoking on the newborn.

JOUBERT: We know that *GFI1* is involved in many developmental processes: It's involved in the development of the inner ear, in pulmonary neuroendocrine cells, influences cell proliferation, apoptosis, differentiation, and many other things. So its application and long-term effects on the children is a little more open-ended than the other two genes that we've mentioned.

LONDON: It's also involved in hematopoiesis, and actually we're appreciating now that the AhR pathway is also involved in that system—so, many important developmental processes.

JOUBERT: Right. There's also the potential for these genes to be interacting, or working in concert on other processes in the body.

AHEARN: Stephanie, if we know the outcomes of smoking during pregnancy can lead to problems like asthma, low birth weight in kids, why is it important to understand the mechanism?

LONDON: Well, there are a number of reasons that it's important to understand the mechanism. I mean, clearly, the bottom-line public health message is that smoking during pregnancy, or at any other time in life, is not a good idea. But, we have identified

a number of health outcomes that appear to be related to smoking during pregnancy. But when, say, the Surgeon General's report reviews the health effects of secondhand smoke, as they did in 2006,[5] there were only a few outcomes where there was really sufficient data for them to say, 'We really think there is a causal association,' because often the type of data that you need to really generate a causal understanding that smoking is causing this condition tend to be kind of hard to come by, and there's always doubt on the part of people looking at this literature saying, 'Well, we know that people who smoke are different than people who don't smoke, and so maybe it's not so much the smoking but something else that people are doing, and so we don't believe that smoking is causing these problems.'

And so when you have mechanistic data, it gives you a layer of confidence that sometimes is difficult or a very, very long-term, time-consuming process to generate with population data. So, the more that we understand about how these things could be occurring, the more we can have confidence that maternal smoking is causing them, and the more we can potentially understand what are the effects at a biological level that could lead us to predict what some health outcomes might be.

AHEARN: Building on that, as these kids get older, what health outcomes are you looking at in the cohort, and how long will you follow them? What are you most curious about?

LONDON: So, the Norwegian Mother and Child cohort is an ongoing pregnancy cohort, and the plan is to follow the children as long as possible. There is definite followup planned through adolescence. We've organized from NIEHS a followup of the children at the age of 7, which is a good age to start looking at the development of asthma, because earlier in life many children have wheezing illness, and only a small proportion of them go on to have asthma at school age when it's easier to diagnose it.

So we're just starting now to look at the data that we've collected from the kids who've already turned age 7 for the development of asthma and allergic conditions. That's what our group has a major focus on. But we're also interested in looking with these methylation data at some other outcomes in the children such as their body mass index, or obesity, and we're interested in looking at birth weight and also the effects of some other pregnancy exposures on the methylation patterns in the cord blood that we've already measured.

AHEARN: I find epigenetics fascinating, because I think it represents the possibility of more clearly connecting our environmental exposures with direct human health outcomes. I'm wondering, what are both of your hopes for this field as it evolves, and what areas are you both most excited to explore?

LONDON: I think we will see a lot of data coming out in the upcoming years about which of these changes can be inherited. Because one of the reasons people are so interested

in epigenetic changes— they are potentially controversial because there's not a lot of direct data, especially in humans, about transgenerational persistence of epigenetic marks. But I think that's something that people are very interested in because of the implications from a public health standpoint.

JOUBERT: And there may even be signatures of exposure that develop as a result of this. And an important thing I think will also be to replicate the findings across various populations with either similar or different exposures, and see whether we can replicate our findings or whether the findings— how the findings compare. And possibly to produce more collaborative groups combining their data sets together.

AHEARN: Stephanie, Bonnie, thanks for joining me.

LONDON: Thank you.

JOUBERT: Thank you.

AHEARN: Stephanie London is the principal investigator for the Genetics, Environment, and Respiratory Disease Group at the National Institute of Environmental Health Sciences.

Bonnie Joubert is a research fellow in the same group.

And that's *The Researcher's Perspective*. I'm Ashley Ahearn. Thanks for downloading!

Ashley Ahearn, host of *The Researcher's Perspective*, has been a producer and reporter for National Public Radio and an Annenberg Fellow at the University of Southern California specializing in science journalism.

References and Notes

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[1] Joubert BR, et al. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environ Health Perspect; http://dx.doi.org/10.1289/ehp.1205412 [online 31 Jul 2012].

[2] "MoBa" is short for *Mor og barn-undersøkelsen*, the Norwegian name for the study.

[3] Monick MM, et al. Coordinated changes in AHRR methylation in lymphoblasts and pulmonary macrophages from smokers. Am J Med Genet B Neuropsychiatr Genet 159B(2):141–151 (2012); http://dx.doi.org/10.1002/ajmg.b.32021.

[4] CpG sites are DNA sequences where a cytosine nucleotide (C) occurs alongside a guanine nucleotide (G) bound by a phosphate (p).

[5] Office of the Surgeon General. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Rockville, MD:U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General (2006).